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ORIGINAL RESEARCH

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Body mass index at birth and early life and colorectal cancer: A two-sample Mendelian randomization analysis in European and East Asian genetic similarity populations

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Summary

Background: Varying obesogenic inherited predisposition in early to later life may differentially impact colorectal cancer (CRC) development. Previous Mendelian randomization (MR) studies, conducted in populations of European genetic similarity, have not observed any significant associations between early life body weight with CRC risk. However, it remains unclear whether body mass index (BMI) at different early lifetime points is causally related with CRC risk in both Europeans and East Asian populations.

Objectives: We conducted a two-sample MR study to investigate potential causal relationships between genetically predicted BMI during early life (birth to 8 years old) and at specific periods (birth, transient, early rise and late rise) and CRC risk.

Methods: Summary data were obtained from genome-wide association study (GWAS) of BMI in 28 681 children from the Norwegian Mother, Father and Child Cohort Study (MoBa) study and applied to CRC GWAS data from European and East Asian descent populations (102 893 cases and 485 083 non-cases).

Results: There were no significant associations observed between early life BMI and CRC risk in European or East Asian populations. The effect estimates were similar in European studies (odds ratio [OR] per a 1-standard deviation [SD] increase: 1.01, 95% confidence interval [CI]: 0.95, 1.07) and in East Asians (OR per a 1-SD increase: 1.02, 95% CI: 0.91, 1.14). Similar nonsignificant associations were found between time of BMI measurement during childhood and cancer-site-specific analyses.

Conclusions: We found little evidence of any associations between early life adiposity on later life CRC risk.

KEYWORDS
colorectal cancer, early life, mendelian randomization, obesity

1 | INTRODUCTION

In recent decades, the increasing prevalence of childhood obesity in most world regions has become an important health problem.[1] There is substantial evidence from observational studies linking early life adiposity with increased risks of chronic diseases, including cancers.[1–4] Therefore, more prevalent obesity from younger ages can have important consequences for population health, regardless of body size in adulthood. Colorectal cancer (CRC) is one of the most common cancer types globally with almost 2 million new cancer cases and over 900 000 related deaths in 2020.[5] CRC has a long latency period meaning that exposures across long life periods occurring many years before diagnosis may be etiologically implicated. It is thus plausible that childhood constitutes a critical period during which adiposity can affect the future development of obesity related cancers in adulthood.[6] Furthermore, obesity during early life has been linked with unfavourable metabolic profiles that may affect cancer risk.[7] Therefore, it is possible that the obesity in early life periods including infancy and childhood may increase the risk of CRC in later life.

Most of the current evidence comes from conventional observational studies. Two meta-analyses have reported positive associations between early life body size and later life CRC risk in both men and women.[8,9] However, causal inference is limited due to the inherent biases of these epidemiological study designs, such as residual confounding, recall bias, selection bias, and reverse causality.[10,11] Mendelian randomization (MR) is an alternative approach to investigate potential causal associations using germline genetic variants as proxies for exposures of interest to allow causal inference between a given exposure and outcome.[12] In contrast to observational analyses, MR analyses are less susceptible to confounding and reverse causality due to the random assortment of alleles at meiosis and germline genetic variants being fixed at conception, and thus unaffected by the disease process.[13] To this end, recently several MR studies have been conducted which did not provide any evidence of effect of early life adiposity on CRC.[14–16] However, some of these studies derived their genetic instruments based on recalled body size information from adults or focused on a specific time point (age of 10)[15,16] or did not conduct sex or CRC site-specific analyses.[14,15]

In the current study, we conducted a two-sample MR analysis to explore potential causal associations between body mass index (BMI) at infancy and early life (up to 8 years) with CRC risk in adulthood. Genetic instruments for BMI were derived from a recent genome-wide association study (GWAS) of 28 681 children.[17] Information on GWAS of CRC risk was obtained from two large CRC European genetic consortia.[18–20] Finally, due to the lack of similar studies in Asian populations, we also conducted an exploratory MR analysis using CRC data from a consortium with participants of East Asian genetic similarity.[21]

2 | METHODS

2.1 | Summary genetic data on early life body size

Genetic variants associated with early life BMI were identified from a recent GWAS of 28 681 children of European genetic similarity from the Norwegian Mother, Father, and Child Cohort Study (MoBa).[17] Length/height and weight of the children were measured at hospitals at birth and during visits in the primary health care system by nurses at 6 weeks, 3, 6 and 8 months, and 1, 1.5, 2, 3, 5, 7 and 8 years of age.[17] A linear mixed model was conducted using BOLT-LMM (v2.3.4) adjusting for batch, sex, pregnancy duration and 10 principal components as covariates used to conduct the GWAS analysis.[17] Forty-six SNPs were identified that were genome-wide significant for at least one time point. In our analysis, we included 39 independent (linkage disequilibrium $R^2 < 0.01$) SNPs with an effect allele frequency over 0.01, out of which eight were exclusively related to BMI at birth and the remaining 31 to early life BMI. Furthermore, three subgroups of SNPs for early life BMI which correspond to distinct biological processes were defined in the original GWAS and were used in our analysis.[17] More specifically, after birth, BMI increases till a maximum value at the age of 9 months and then followed by a gradual decline reaching a minimum point around the 5–6 years of age. These two time points are known as the adiposity peak (AP) and adiposity rebound (AR) points. Consequently, the 'transient' group (17 SNPs) includes SNPs with no effect at birth, a peak association during infancy or early childhood, and little or no effect after the AR point. The 'early rise' group (10 SNPs) includes SNPs that show a gradually stronger association with BMI from infancy into childhood, plateauing at AR and 7 to 8 years of age. Finally, the 'late rise' group (4 SNPs) includes SNPs that show little to no association before AR while they show a large increase after this point. The 39 SNPs used as instruments were identified in 37 loci demonstrating a small overlap between the phenotypes. Tables S1 and S2 include the SNPs that were used in our analysis.

2.2 | Summary genetic data on colorectal cancer (CRC)

Summary data for the associations of the early life BMI associated genetic variants with CRC risk in participants of European and East Asian genetic similarity were obtained from CRC GWAS studies within three genetic consortia. For overall CRC, we used summary-level data from a meta-analysis of 16 GWASs, including 160 527 adults (73 673 cases and 86 854 controls) of European genetic similarity.[20] Data on sex and site-specific CRC (colon, proximal colon, distal colon and rectum) were collected from a meta-analysis of three genetic consortia within ColoRectal Transdisciplinary Study (CORECT), the Colon Cancer Family Registry (CCFR), and the Genetics and Epidemiology of Colorectal Cancer (GECCO).[18] Finngen combined imputed genotype data integrated from Finnish biobanks and digital health registry records, and it is frequently updated.[19] The version (R10) includes 412 181 participants out of which 4143 developed colon cancer and 2490 rectal cancer. (https://r8.risteys.finngen.fi/phenocode/C3_COLORECTAL). Summary data from Finngen was used only in the site-specific analyses as Finngen was also part of the latest CRC GWAS study we used in the overall CRC analysis. The Asia Colorectal Cancer Consortium (ACCC) includes 72 272 participants (23 572 cases and 48 700 controls) of East Asian genetic similarity from 15 studies conducted in China, Japan and South Korea.[22] All cancer estimates from the three consortia are presented in the Tables S3–S8.

Regarding the summary data used in the MR analyses, informed consents were obtained from the participants and study protocols were approved by respective institutional review boards.[17–20,22]

3 | STATISTICAL ANALYSIS

3.1 | Mendelian randomization

A two-sample MR approach using summary data and the random effects inverse variance weighting (IVW) method was implemented. MR studies depend on three main assumptions for their estimates to be valid: (1) the genetic instrument is strongly associated with the exposure; (2) the genetic instrument is not associated with any potential confounder of the exposure—outcome association; and (3) the genetic instrument does not affect the outcome independently of the exposure (i.e., exclusion of horizontal pleiotropy). The strength of each genetic instrument can be evaluated through the F-statistic using the following formula: $F = R^2(N-2)/\left(1-R^2\right)$, where R^2 is the proportion of the variability of the exposure explained by each instrument and N the sample size of the GWAS for the SNP- early life BMI association. To calculate the R^2 for the genome-wide significant SNPs the following formula was used: $2 \times EAF \times (1-EAF) \times beta^2$, where EAF is the effect allele frequency and beta is the estimated genetic effect on BMI. Cochran's Q was computed to quantify heterogeneity across the individual causal effects, with a p-value ≤0.05 indicating the presence of pleiotropy.[23,24]

Several sensitivity analyses were conducted to identify and correct for the presence of horizontal pleiotropy in our results. MR-Egger regression provides valid MR estimates in the presence of horizontal pleiotropy when the pleiotropic effects of the genetic variants are independent from the genetic associations with the exposure.[25]

TABLE 1 Sample size and statistical power in Mendelian randomization (MR) study of early body mass index (BMI) and colorectal cancer (CRC) risk.

Exposure	Study	Sample size	Ratio of cases to controls	Selected scenarios[a]				
				OR = 1.05	OR = 1.1	OR = 1.15	OR = 1.2	OR = 1.25
Birth	CRC consortium	160 527	0.85	0.28	0.77	0.98	1.00	1.00
	ACCC	72 272	0.47	0.13	0.39	0.69	0.89	0.97
Early life	CRC consortium	160 527	0.85	0.67	1.00	1.00	1.00	1.00
	ACCC	72 272	0.47	0.32	0.82	0.99	1.00	1.00
Transient	CRC consortium	160 527	0.85	0.39	0.91	1.00	1.00	1.00
	ACCC	72 272	0.47	0.18	0.53	0.85	0.97	1.00
Early rise	CRC consortium	160 527	0.85	0.28	0.77	0.98	1.00	1.00
	ACCC	72 272	0.47	0.13	0.39	0.69	0.89	0.97
Late rise	CRC consortium	160 527	0.85	0.16	0.48	0.80	0.95	0.99
	ACCC	72 272	0.47	0.09	0.22	0.41	0.62	0.79

Note: The numbers under the OR columns in the selected scenarios section correspond to the statistical power of our analysis for each of the five exposure variables given a specific value of OR.

Abbreviation: ACCC, Asian colorectal cancer consortium; CRC, colorectal cancer; OR, odds ratio.

[a]Type 1 error of 5% and a proportion of variance explained equal to 2%, 6%, 3%, 2% and 1% are assumed for birth, overall early life, transient, early rise and late rise periods, respectively.

Deviations from zero for the intercept test denote the presence of horizontal pleiotropy across the genetic variants. In such a case, the slope of the MR-Egger regression provides valid MR estimates when the pleiotropic effects of the genetic variants are independent from the genetic associations with the exposure.[25,26] Additionally, the I^2_{GX} statistic was calculated to estimate the expected relative bias of the MR-Egger causal estimate in the context of a two-sample MR.[27] Moreover, causal estimates were also computed using the weighted-median method that provides valid MR estimates under the presence of horizontal pleiotropy when up to 50% of the included instruments are invalid.[28] The MR pleiotropy residual sum and outlier test (MR-PRESSO) was also used to assess the presence of pleiotropy. The MR-PRESSO test relies on a regression framework to identify outlying genetic variants which may potentially be pleiotropic. Thereupon, we repeated the analysis after excluding these outlying variants.[29]

The statistical power for the MR analysis was calculated a priori using an online tool at https://sb452.shinyapps.io/power/.[30] Given a type 1 error of 5%, for early life BMI an expected OR per 1 standard deviation (SD) ≥1.06 and ≥1.1 was needed to have adequate statistical power (>80%) in GECCO and ACCC, respectively. Table 1 presents the power estimates under different scenarios for the five exposures. All the results correspond to a 1-SD increase in early life BMI.

As a final step, we conducted a random effects meta-analysis in the cases of colon and rectal cancer combining the results from CCFR, CORECT and GECCO with Finngen to get an overall estimate using the metan command in Stata (College Station, Texas), and heterogeneity between the two studies was quantified using the I^2 statistic.[31]

MR analyses were performed using R (Vienna, Austria) version 4.3.3, using the "MendelianRandomization" (version 0.9) package. The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines.

4 | RESULTS

Figure 1 shows the results for overall early life BMI where no relationships were observed between genetically predicted BMI in early life and CRC risk. The odds ratio (OR) per 1-SD increase of overall early life BMI in the CRC consortium was 1.01 (95% confidence interval [CI]: 0.95, 1.07). Similar non-significant risk estimates were also observed in the site-specific analyses (Figure 1).

Examination of BMI at specific time periods also indicated no evidence of an association. Although, in Finngen some opposite but imprecise effects were observed for rectal cancer between genetically predicted BMI in the early rise phase (OR: 0.79, 95% CI: 0.55, 1.11) compared with the late rise phase (OR: 1.27, 95% CI: 0.84, 1.93) with overlapping CIs (Figure 2 and Tables S9–S13). The sex-specific analysis in GECCO also did not identify any associations of birth or early life BMI with CRC risk (Figure S1). The analysis in ACCC also did not indicate any apparent effects of early life BMI and overall CRC risk (OR: 1.02, 95% CI: 0.91, 1.14) (Figure 1).

Based on the F-statistics, the genetic instruments were deemed strong (F-statistic all ≥35) (Table S1). There was some evidence of heterogeneity mainly in the analysis of birth BMI (maximum p-value for the Q statistic 0.003) (Table S13). Additionally, Egger's intercept test showed some evidence of directional pleiotropy in the analyses of overall early life BMI and risk of overall colorectal and colon cancer (Table S9). The MR-Egger regression effect for colon cancer was stronger than the IVW approach (OR: 1.25, 95% CI: 1.02, 1.52)

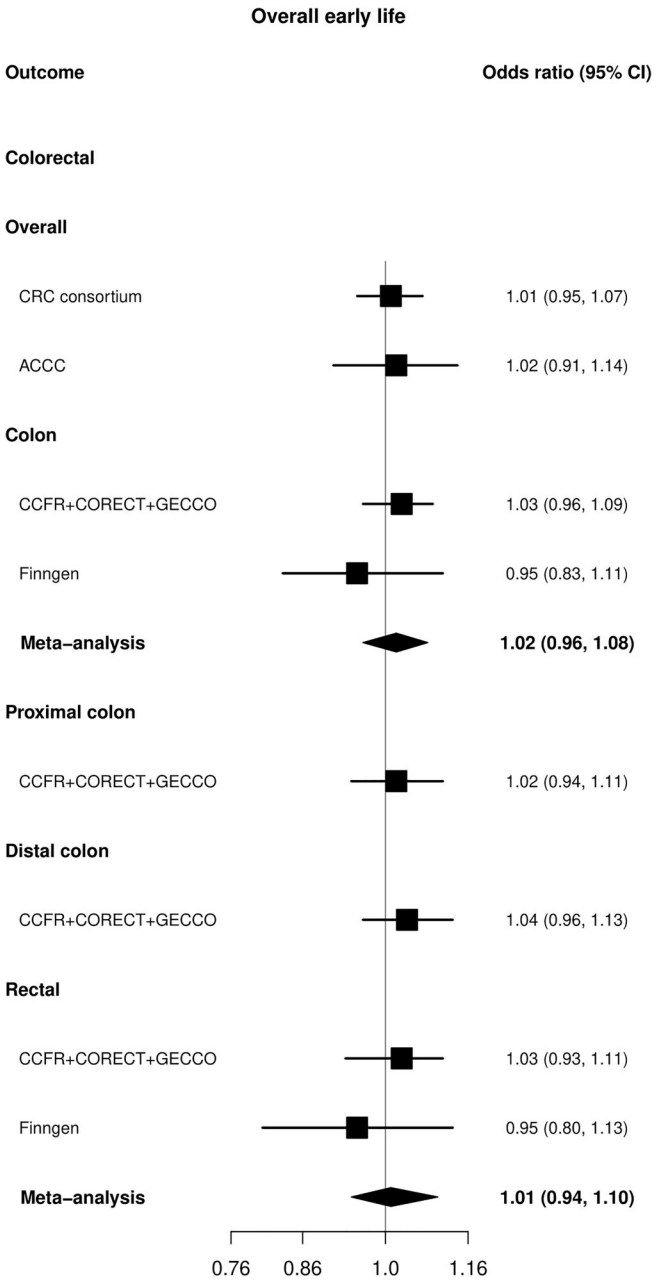

FIGURE 1 Mendelian randomization (MR) analysis for early life BMI (31 SNPs) in relation to colorectal cancer (CRC) in GECCO, Finngen and Asia Colorectal Cancer Consortium (ACCC). The *x* axis corresponds to an OR change per 1 standard deviation increase in BMI. The MR result corresponds to a random effects model. OR, odds ratio (black filled square); 95% CI, 95% confidence interval (black line); SNP, single nucleotide polymorphism.

(Table S9). However, the I^2_{GX} statistic was low (<55%) meaning that there is evidence of weak instrument bias in these results and additionally the weighted median approach also did not show any positive effects. The MR-PRESSO technique identified two outlying SNPs (rs1032296 and rs1772945) both present in the analysis of overall early life and transient BMI and overall CRC risk; however, their exclusion had minimal effect on the observed associations (Tables S9 and S10). Additionally, five out of the eight SNPs (rs11708067, rs1482853, rs11187129, rs7310615 and rs739669) in the analysis of birth BMI were also identified as outliers; however, the inference did not change after their exclusion from the genetic instrument (OR: 1.08, 95% CI: 0.90, 1.30) (Table S13).

5 | DISCUSSION

In the current study, genetically predicted early life BMI, both in overall and measured at different time periods, did not show a significant association with CRC risk in adulthood. Furthermore, our analysis in a population of Asian descent also did not identify any potential associations either.

Recently, several MR studies have addressed this question using different approaches. The first study examined the associations between childhood obesity and cancer risk, creating a genetic instrument of 15 SNPs from a GWAS of 47 541 children from the Early Growth Genetics consortium.[14] The results of this study did not support any positive relationship between genetically predicted childhood BMI and overall CRC (OR: 1.11, 95% CI: 0.93, 1.32). However, the SNPs in this GWAS were derived from a meta-analysis of studies where the phenotype analysed was BMI at the latest time point between 2 and 10 years.[32] Therefore, we cannot exclude potential bias in the results given the mixing of results coming from studies with different protocols using different time-specific endpoints. Two additional MR studies using an instrument of body size at the age of 10 from UK Biobank (UKBB) also did not report any significant associations after adjusting for body size during adulthood, although there was a weak evidence of a positive effect for distal colon cancer (OR: 1.27, 95% CI: 0.90, 1.77).[15,16] However, under the univariable MR framework positive effect estimates were found for overall colon (OR: 1.16, 95% CI: 1.00, 1.35) and distal colon (OR: 1.25, 95% CI: 1.04, 1.51) cancer.[16] In our analysis, we did not observe similar results either for overall early life or time-period specific BMI. Potential reasons could be the difference in the size between the two GWASs used to obtain the SNPs included in the genetic instrument as well as the different phenotypes. The previous publication used the summary of a much larger GWAS of early life body size within the UKBB thus increasing the power of the analysis. Moreover, in contrast to our analysis where SNPs of measured BMI were used, the exposure in UKBB was based on a self-reported questionnaire of early life body type at the age of 10 years (thinner, plumper or about average) than on direct measurements, which could potentially introduce recall bias in the measurements.

There is also additional evidence from observational studies. Two recent meta-analyses have both reported an increased CRC risk in adulthood for elevated BMI assessed during adolescence or early adulthood (maximum age: 30 years). More specifically, the first meta-analysis found that men with obesity had 39% higher CRC risk during late adulthood compared with men without obesity while the risk was 19% in women.[8] Furthermore, the second meta-analysis reported that each 5 kg/m^2 increase in BMI was associated

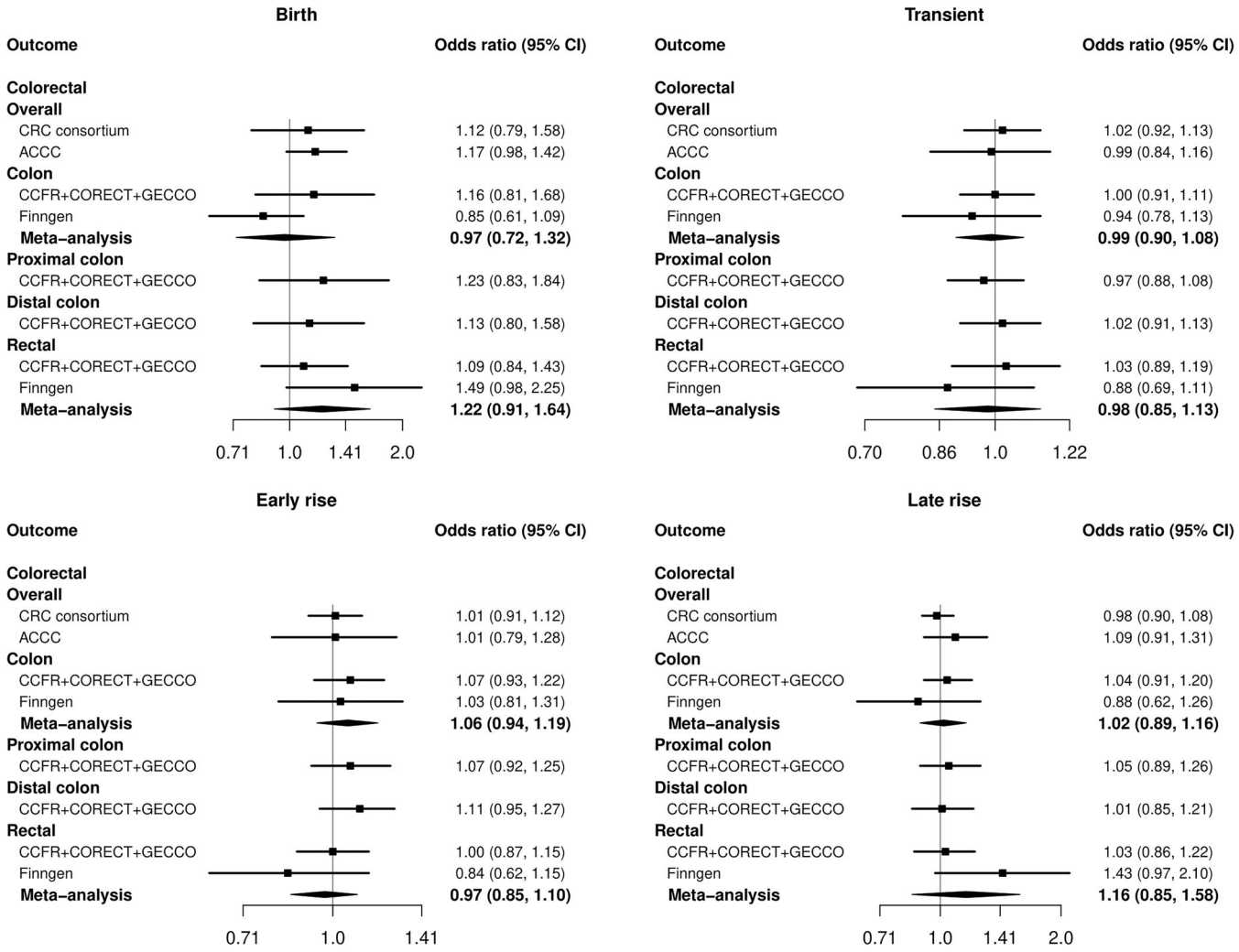

FIGURE 2 Mendelian randomization (MR) analysis for BMI at birth (8 SNPs) as well as in specific time periods (transient: 17 SNPs, early rise: 10 SNPs, late rise: 4 SNPs) in relation to colorectal cancer (CRC) in GECCO, Finngen and Asia Colorectal Cancer Consortium (ACCC). The *x* axis corresponds to an OR change per 1 standard deviation increase in BMI. The MR result corresponds to a random effects model. OR, odds ratio (black filled square); 95% CI, 95% confidence interval (black line); SNP,- single nucleotide polymorphism.

with a 13% higher CRC risk in men and women combined, with the risk being higher in men than in women.[9] An additional large Israeli study of almost 1.8 million men and women reported that being overweight and obese at adolescence was linked with higher colon cancer risk for both men (Hazard ratio [HR] for overweight: 1.53, 95% CI; 1.28, 1.84; HR for obesity: 1.54, 95% CI: 1.15, 2.06) and women (HR for overweight: 1.54, 95% CI: 1.22, 1.93; HR for obesity: 1.51, 95% CI: 0.89, 2.57). However, information on important potential confounders such as adult BMI, diet, alcohol, and smoking was missing.[33] Additionally, our study focused on an earlier time point than most of the observational studies. Also, contrary to MR analyses, these studies can also be prone to additional biases like recall and selection bias due to their observational nature as mentioned earlier.

To our knowledge, there are no studies conducted in Asian populations regarding the role of obesity during early life and CRC risk. However, current evidence from MR studies supports a positive link between adult adiposity and CRC, aligning with results from studies conducted in populations of European genetic similarity. More specifically, a recent MR study in Japanese participants indicated that a one-unit increase in genetically predicted BMI increased CRC risk by 13% (OR: 1.13, 95% CI: 1.06, 1.20).[34] Our results in ACCC did not find any associations between early life BMI and CRC; however, GWAS studies of early life BMI in populations of East Asian genetic similarity are required to give more precise answers.

To our knowledge, the current MR study is the first one that tried to investigate the role of early life BMI at different time periods and CRC in adulthood using genetic instruments strongly associated with early life BMI, as denoted by the large values for the F-statistic. We also conducted tumour subsite specific analyses to further inspect the role of early life adiposity on CRC risk. Another strength comes from the MoBa study which was able to conduct detailed time-specific analyses rather than just combining data from studies performed under different protocols and time points.[17] Furthermore, there was no

overlap between the exposure and outcome studies which could lead to biased results.[35] Additionally, measured rather than self-reported BMI was used in the body size GWAS, which is less likely prone to recall bias, while the inclusion of sex-specific and cancer-site-specific analyses allowed us to conduct more detailed analyses. Also, MR-Egger and MR-PRESSO methods were also applied to examine the robustness of our results given that in general the BMI-related variants tend to be pleiotropic. Finally, the MR design is less prone to the limitations of observational studies while the consistency among the different MR methods applied strengthens the robustness of the results.

The main limitation was the small sample size of the MoBa study which resulted in a relatively small number of identified SNP that could be used in our analysis. A direct consequence of that is the limited statistical power of our analysis, especially for the different cancer subtypes. However, this detailed data collection at several time points since birth is valuable and future, larger GWAS studies should follow the same paradigm which will allow the identification of a larger number of genetic variants. The genetic instruments were selected from a single cohort of Norwegian children, and further research is needed to evaluate the generalizability of the results to other populations. Additionally, body composition as well as the allele frequencies of the SNPs that were used in the MR analysis are in general different between populations of European and East Asian genetic similarity. Given differences in linkage disequilibrium across different population it is likely that the instrument is weaker in East Asians. Similarly, we cannot exclude the presence of confounding due to population stratification in the analysis of East Asians since the SNP-early life BMI GWAS was undertaken in a different study population than the SNP–CRC GWAS.[13] Consequently, caution is needed when interpreting the results from the ACCC analysis. As mentioned earlier, GWAS of early BMI in populations of Asian genetic similarity are needed to produce more valid results. Unfortunately, we are not aware of any data in East Asian populations that have BMI measured early in life and have GWAS data to assess if our instrument is stable in East Asians. Therefore, this analysis is more of an exploratory nature untill such GWAS studies become available. In our analysis, seven SNPs mainly in "late rise" cluster have also been linked with BMI during adulthood.[17] However, our sensitivity analyses generated results consistent with the main findings. Additionally, given the null associations, any effect of adult BMI is minimal.

In summary, our current study did not find any statistically significant support for causal effects of BMI at birth or during childhood with risk of CRC in adulthood. Larger GWAS studies from different populations and with measures of BMI at different time points during childhood are needed to better identify potential critical periods of weight and weight change in early life in relation to CRC development in adulthood.

AUTHOR CONTRIBUTIONS

Concept and design: Hughes, Jenab and Murphy. Statistical analysis: Papadimitriou. Writing—drafting of the manuscript: Papadimitriou. Writing—review and editing: all authors. Data curation: Zheng and Peters.

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The necessary data to replicate our MR analysis are included in the supplementary material.

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REFERENCES

1. Collaborators GBDO, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27.
2. Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. Adolescent overweight and future adult coronary heart disease. *N Engl J Med*. 2007;357(23):2371-2379.
3. Hannon TS, Rao G, Arslanian SA. Childhood obesity and type 2 diabetes mellitus. *Pediatrics*. 2005;116(2):473-480.
4. Xue F, Rosner B, Eliassen H, Michels KB. Body fatness throughout the life course and the incidence of premenopausal breast cancer. *Int J Epidemiol*. 2016;45(4):1103-1112.
5. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
6. Wei EK, Wolin KY, Colditz GA. Time course of risk factors in cancer etiology and progression. *J Clin Oncol*. 2010;28(26):4052-4057.
7. Biro FM, Wien M. Childhood obesity and adult morbidities. *Am J Clin Nutr*. 2010;91(5):1499S-1505S.
8. Garcia H, Song M. Early-life obesity and adulthood colorectal cancer risk: a meta-analysis. *Rev Panam Salud Publica*. 2019;43:e3:1-8.
9. Hidayat K, Yang CM, Shi BM. Body fatness at an early age and risk of colorectal cancer. *Int J Cancer*. 2018;142(4):729-740.
10. Davey Smith G, Ebrahim S. Epidemiology—is it time to call it a day? *Int J Epidemiol*. 2001;30(1):1-11.
11. Lawlor DA, Davey Smith G, Kundu D, Bruckdorfer KR, Ebrahim S. Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet*. 2004;363(9422):1724-1727.
12. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22.
13. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey SG. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. 2008;27(8):1133-1163.
14. Fang X, Wang X, Song Z, et al. Causal association of childhood obesity with cancer risk in adulthood: a mendelian randomization study. *Int J Cancer*. 2021;149(7):1421-1425.
15. Mariosa D, Smith-Byrne K, Richardson TG, et al. Body size at different ages and risk of 6 cancers: a mendelian randomization and prospective cohort study. *J Natl Cancer Inst*. 2022;114(9):1296-1300.
16. Papadimitriou N, Bull CJ, Jenab M, et al. Separating the effects of early and later life adiposity on colorectal cancer risk: a mendelian randomization study. *BMC Med*. 2023;21(1):5.
17. Helgeland O, Vaudel M, Sole-Navais P, et al. Characterization of the genetic architecture of infant and early childhood body mass index. *Nat Metab*. 2022;4(3):344-358.
18. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet*. 2019;51(1):76-87.
19. Kurki MI, Karjalainen J, Palta P, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508-518.
20. Fernandez-Rozadilla C, Timofeeva M, Chen Z, et al. Deciphering colorectal cancer genetics through multi-omic analysis of 100,204 cases and 154,587 controls of European and east Asian ancestries. *Nat Genet*. 2023;55(1):89-99.
21. Lu Y, Kweon SS, Tanikawa C, et al. Large-scale genome-wide association study of east Asians identifies loci associated with risk for colorectal cancer. *Gastroenterology*. 2019;156(5):1455-1466.

22. Lu Y, Kweon SS, Cai Q, et al. Identification of novel loci and new risk variant in known loci for colorectal cancer risk in east Asians. *Cancer Epidemiol Biomarkers Prev*. 2020;29(2):477-486.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
24. Bowden J, del Greco MF, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data mendelian randomization. *Stat Med*. 2017;36(11):1783-1802.
25. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *Int J Epidemiol*. 2015;44(2):512-525.
26. Burgess S, Thompson SG. Interpreting findings from mendelian randomization using the MR-egger method. *Eur J Epidemiol*. 2017;32(5):377-389.
27. Bowden J, del Greco MF, Minelli C, Davey Smith G, Sheehan NA, Thompson JR. Assessing the suitability of summary data for two-sample mendelian randomization analyses using MR-egger regression: the role of the I^2 statistic. *Int J Epidemiol*. 2016;45(6):1961-1974.
28. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304-314.
29. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693-698.
30. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497-1501.
31. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
32. Felix JF, Bradfield JP, Monnereau C, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. *Hum Mol Genet*. 2016;25(2):389-403.
33. Levi Z, Kark JD, Katz LH, et al. Adolescent body mass index and risk of colon and rectal cancer in a cohort of 1.79 million Israeli men and women: a population-based study. *Cancer*. 2017;123(20):4022-4030.
34. Suzuki S, Goto A, Nakatochi M, et al. Body mass index and colorectal cancer risk: a mendelian randomization study. *Cancer Sci*. 2021;112(4):1579-1588.
35. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample mendelian randomization. *Genet Epidemiol*. 2016;40(7):597-608.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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